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(54) Title: MEDICAMENTS COMPRISING 5HT1-LIKE RECEPTOR AGONISTS WITH AN INCREASED ABSORPTION

(57) Abstract

The invention relates to a method improving the absorption of compounds which act as $5HT_1$-like receptor agonists following oral or intranasal administration. The invention also provides pharmaceutical compositions for oral or intranasal administration of $5HT_1$-like receptor agonists and paracellular absorption enhancers. The paracellular absorption enhancers increase the rate of absorption of the $5HT_1$-like receptor agonist. Suitable $5HT_1$-like receptor agonists for use in the invention include sumatriptan, naratriptan and 4-[3-(trans-3-dimethylaminocyclobutyl)-1H-indol-5-ylmethyl]-(4S) oxazolidin-2-one.

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MEDICAMENTS COMPRISING 5HT1-LIKE RECEPTOR AGONISTS WITH AN INCREASED ABSORPTION

The present invention relates to a method for improving the absorption of compounds which act as agonists at $5HT_1$-like receptors, e.g. sumatriptan and naratriptan 4-[3-(trans-3-dimethylaminocyclobutyl)-1H-indol-5-ylmethyl]-(4S) oxazolidin-2-one following oral or intranasal administration. More specifically, the present invention provides pharmaceutical compositions of $5HT_1$-like receptor agonists, particularly compositions for oral or intranasal administration.

$5\text{-}HT_1$-like receptors are located, for example, in the dog saphenous vein and the $5\text{-}HT_1$-like receptor agonists with which the present invention is concerned contract the dog saphenous vein. Such compounds may therefore be identified by their contractile effect on the dog isolated saphenous vein strip as described, for example, by Apperley et al., Br. J. Pharmacol, 68, 215-224 (1980). Compounds which are selective $5\text{-}HT_1$-like receptor agonists have also been found to selectively constrict the carotid arterial bed of the anaesthetised dog.

A variety of compounds which selectively constrict the dog isolated saphenous vein strip and which constrict the carotid arterial bed of the anaesthetised dog have been described in the art. These include indole derivatives such as those disclosed inter alia in published British Patent Specifications Nos. 2082175, 2081717, 2083463, 2124210, 2150932, 2162522, 2168347, 2168973, 2185020, 2186874, 2191488, 2208646, published European Patent Specifications Nos. 147107, 237678, 242939, 244085, 225726, 254433, 303506, 313397, 354777, 382570, 464558, 506363, 506369, 450238, 451022, 451008, 478954, 438230, 494774, 497512, 501568 and published International patent application Nos. WO92/11013, W092/11014, WO92/06973, WO93/00086, WO92/13856,

WO93/00094, WO91/18897, WO93/00333 and WO94/02477 which specifications are incorporated herein by reference.

A particular compound for use in the instant invention is 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide and physiologically acceptable salts and solvates thereof as disclosed in GB2162522. This compound is also known as sumatriptan. "Sumatriptan" when used hereinafter means the compound 3-[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide and its physiologically acceptable salts and solvates thereof.

Another particular compound for use in the instant invention is (N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide and physiologically acceptable salts and solvates thereof as disclosed in GB2208646. This compound is also known as naratriptan. "Naratriptan" when used hereinafter means the compound (N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide and its physiologically acceptable salts and solvates thereof.

An additional specific compound which acts as an agonist at $5HT_1$-like receptors and is of use in the instant invention is 4-[3-(trans-3-dimethylaminocyclobutyl)-1H-indol-5-ylmethyl]-(4S) oxazolidin-2-one (described in WO95/20588).

Reference hereinafter to "$5HT_1$-like receptor agonists" means sumatriptan, naratriptan, 4-[3-(trans-3-dimethylaminocyclobutyl)-1H-indol-5-ylmethyl]-(4S) oxazolidin-2-one, the compounds generically and specifically disclosed in the patent specifications listed hereinbefore and physiologically acceptable salts and solvates thereof.

Compounds which act as agonists at $5HT_1$-like receptors exhibit selective vasoconstrictor activity. They are useful in the treatment of cephalic pain resulting from dilation of the cranial vasculature, in particular migraine. The compounds are also useful in the treatment of other conditions associated with cephalic pain such as cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, headache associated with substances or their withdrawal (for example drug withdrawal) and tension headache. Also, the compounds are useful in the treatment of elevated intraocular pressure, in particular glaucoma e.g. high tension glaucoma and low tension glaucoma.

$5HT_1$-like receptor agonists may be administered orally and, following oral administration, it is believed that they are absorbed paracellularly (i.e. through the tight junctions between cells of the intestinal mucosa). It is also believed that, following intranasal administration, $5HT_1$-like receptor agonists are absorbed paracellularly. Although $5HT_1$-like receptor agonists such as sumatriptan and naratriptan are sufficiently well-absorbed following oral or intranasal administration to effect treatment, enhancement of drug absorption would be advantageous since this would enable lower doses to be effective (enhanced extent of absorption) and would provide more rapid relief from symptoms (enhanced rate of absorption).

A method of significantly enhancing the absorption of $5HT_1$-like receptor agonists following oral or intranasal administration has now been found. This method involves administration of the $5HT_1$-like receptor agonist together with one or more further compounds which, without wishing to be bound by theory, are believed to increase paracellular absorption. These further compounds are hereinafter referred to as "paracellular absorption enhancers".

Thus the present invention provides, in one aspect, the use of a $5HT_1$-like receptor agonist and one or more paracellular absorption enhancers in the manufacture of medicaments for simultaneous, separate or sequential use for the treatment of cephalic pain, e.g. migraine, and elevated intraocular pressure. Suitably the $5HT_1$-like receptor agonist is sumatriptan, naratriptan or 4-[3-(trans-3-dimethylaminocyclobutyl)-1H-indol-5-ylmethyl]-(4S)-oxazolidin-2-one. In a preferred embodiment the $5HT_1$-like receptor agonist is sumatriptan or naratriptan, with naratriptan being particularly preferred.

In a further aspect, the present invention provides the use of a $5HT_1$-like receptor agonist, for example sumatriptan, naratriptan or 4-[3-(trans-3-dimethylaminocyclobutyl)-1H-indol-5-ylmethyl]-(4S)-oxazolidin-2-one, and one or more paracellular absorption enhancers in the manufacture of medicaments for simultaneous, separate or sequential use for the treatment of cephalic pain, e.g. migraine, and elevated intraocular pressure, characterised in that the paracellular absorption enhancer(s) significantly enhances the absorption of the $5HT_1$-like receptor agonist. The use of sumatriptan or naratriptan, particularly naratriptan, is preferred.

In a further aspect, the invention provides a method of treatment of cephalic pain, e.g. migraine, and elevated intraocular pressure, comprising orally or intranasally administering to a sufferer an effective amount of a pharmaceutical composition comprising a $5HT_1$-like receptor agonist, or a physiologically acceptable salt thereof, and one or more paracellular absorption enhancers, wherein the paracellular absorption enhancer significantly enhances the absorption of the $5HT_1$-like receptor agonist. Suitably, sumatriptan, naratriptan or 4-[3-(trans-3-dimethylaminocyclobutyl)-1H-indol-5-ylmethyl]-(4S)-oxazolidin-2-one is administered, with sumatriptan and naratriptan being preferred. Intranasal administration of naratriptan is particularly preferred.

The term "paracellular absorption enhancer" as used herein encompasses any compound which is believed to enhance paracellular absorption. For example, suitable paracellular absorption enhancers are those which occur naturally in nutrients. Paracellular absorption enhancers include carbohydrates such as monosaccharides, e.g. glucose, galactose, mannose, 3-0-methyl glucose, xylose, ribose, arabinose, ribulose, fructose and sorbose. The monosaccharides may be employed in either their D- or L- forms. Where the monosaccharide is naturally occuring, the naturally occuring form is preferred.

Preferred paracellular absorption enhancers include glucose, e.g. D-glucose. A further preferred group of paracellular absorption enhancers includes galactose, e.g. D-galactose, mannose, e.g. D-mannose, 3-0-methyl glucose, e.g 3-0-methyl D-glucose, xylose, e.g. D-xylose.

It will be appreciated that the paracellular absorption enhancer(s) employed in the instant invention will be of the reversible type i.e. one whose absorption enhancement effect rapidly diminishes when it is no longer present at the site of action. All of the paracellular absorption enhancers specifically mentioned above are of the reversible type.

The paracellular absorption enhancers may be used alone or in combination.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

It is preferred that the $5HT_1$-like receptor agonists, e.g. sumatriptan or naratriptan, should be employed in the compositions according to the invention in the form of a physiologically acceptable salt. In the case of sumatriptan and

naratriptan such salts include salts of inorganic or organic acids such as hydrochloride, hydrobromide, sulphate, nitrate, phosphate, formate, mesylate, citrate, benzoate, fumarate, maleate and succinate salts. Most preferably, for oral administration, sumatriptan (3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide) will be employed in the compositions according to the invention in the form of its succinate (1:1) salt. For intranasal administration, sumatriptan will most preferably be employed in the compositions according to the invention in the form of its sulphate salt (2:1) as described in International Patent Application No. WO92/10477 which is incorporated herein by reference. Naratriptan is preferably in the form of its hydrochloride salt for oral administration. The hydrochloride salt of naratriptan is also preferred for intranasal administration. Another preferred salt of naratriptan for intranasal administration is the aspartate. The maleate salt of naratriptan is particularly preferred for intranasal administration.

It will be appreciated that the paracellular absorption enhancers enhance absorption of the $5HT_1$-like receptor agonists following dissociation from their salts.

As mentioned hereinbefore, paracellular absorption enhancers have been found to significantly enhance the absorption of $5HT_1$-like receptor agonists following oral or intranasal administration. Surprisingly, both the extent and rate of absorption are enhanced. In the case of sumatriptan, and especially naratriptan, the extent and rate of absorption are enhanced to an unexpected, surprisingly large degree.

Thus, according to a further aspect, the present invention provides a method of significantly enhancing the rate of absorption of a $5HT_1$-like receptor agonist, for example sumatriptan, naratriptan or 4-[3-(trans-3-dimethylaminocyclobutyl)-1H-

indol-5-ylmethyl]-(4S) oxazolidin-2-one or a physiologically acceptable salt thereof, following oral or intranasal administration by simultaneous, separate or sequential administration of the $5HT_1$-like receptor agonist with one or more paracellular absorption enhancers. Intranasal administration of naratriptan is particularly preferred.

The $5HT_1$-like receptor agonist and one or more paracellular absorption enhancers may be co-administered in the form of separate pharmaceutical compositions for simultaneous and/or sequential use. Preferably, the $5HT_1$-like receptor agonist and paracellular absorption enhancer(s) are administered as a single pharmaceutical composition for oral or intranasal use comprising effective amounts of the active ingredient.

Thus, according to a further aspect, the invention provides a pharmaceutical composition for oral or intranasal use comprising a $5HT_1$-like receptor agonist and one or more paracellular absorption enhancers. Suitable compositions comprise, sumatriptan, naratriptan or 4-[3-(trans-3-dimethylaminocyclobutyl)-1H-indol-5-ylmethyl]-(4S) oxazolidin-2-one. Compositions comprising sumatriptan or naratriptan are preferred.

In the case of naratriptan, pharmaceutical compositions for intranasal use are particularly preferred.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium

hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Suitable methods of formulation are known in the art and include those methods described in UK patent Specification Nos 2250917 (effervescent tablets), 2254784 (film-coated tablet), International Patent Specification Nos WO93/24116 (chewable capsules), and French Patent Specification No 9306435 (non-effervescent granules), which are incorporated herein by reference.

For intranasal administration the pharmaceutical formulations may take the form of, for example, a liquid in the form of, for example, a solution, suspension or emulsion, presented in the form of a spray or drops, or as a powder. Preferably the preparation for intranasal administration is delivered in the form of a spray or aerosol from an insufflator or from a pressurised pack or nebuliser with the use of a suitable propellant. Suitable methods of formulation are known in the art and include those methods described in International Patent Specification No WO92/10477 (intranasal sumatriptan formulation) which is incorporated herein by reference.

The paracellular absorption enhancer(s) may be incorporated into the above-mentioned formulations according to conventional procedures.

$5HT_1$-like receptor agonists and paracellular absorption enhancer(s) may, if desired, be administered in combination with one or more other therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art. For example, the $5HT_1$-like receptor agonist and paracellular absorption enhancer(s) may be administered in combination with an anti-emetic. For example, a suitable formulation of this is described in European Patent Specification No EP0433043. The paracellular absorption enhancer(s) may be incorporated into the above-mentioned formulations according to conventional procedures.

The ratio of $5HT_1$-like receptor agonist to paracellular absorption enhancer(s) used in the method or compositions according to the invention is in the range of 1:1 to 1:1000 (by weight), such as 1:1 to 1:50 or 1:150 (by weight), for example 1: 5 (by weight).

The amount of paracellular absorption enhancer used in the oral formulations according to the instant invention is in the range of 1 to 10g, e.g. 1 to 3g, per dosage unit.

The amount of $5HT_1$-like receptor agonist used in the oral formulations according to the instant invention is preferably in the range of 0.5 to 250mg per dosage unit. For example, the amount of sumatriptan in the composition is preferably in the range of 1 to 200mg, more preferably 5 to 100mg, such as 10 to 50mg expressed as the weight of free base. The amount of naratriptan in the

composition is preferably in the range of 0.1 to 50mg, such as 5 to 20mg, e.g. 0.25 to 2.5mg expressed as the weight of free base.

The unit dose (for example contained in one tablet according to the invention) may be administered for example, 1 to 4 times a day, preferably once or twice a day.

For intranasal administration, a convenient unit dose contains the active ingredient in an amount from 0.05mg to 100mg, preferably in the range of 1 to 60mg, most preferably 2 to 40mg, which may be administered to either one or both nostrils. Most preferably, when the active ingredient is sumatriptan sulphate (2:1), 2.5mg to 25mg of the active ingredient is administered in a single dose to one nostril. When the active ingredient is naratriptan hydrochloride, naratriptan aspartate or naratriptan maleate, preferably 0.1mg to 1mg of the active ingredient is administered in a single dose to one nostril.

The following are illustrations of non-limiting examples of pharmaceutical compositions according to the invention.

Example 1

Powder for Oral Administration

	Unit dose (mg per sachet)
3[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide(1 : 1) succinate	140*
D-Glucose	1000
Aspartame	40
Flavour	16

*Equivalent to 100mg base

The ingredients are thoroughly mixed together in a suitable blender under anhydrous conditions and filled into an aluminium foil sachet. The sachet is sealed after filling in conventional manner.

The contents of the sachet are dissolved in a glass of drinking water immediately prior to oral administration.

Example 2

Granules for Oral Administration	Unit dose (mg per sachet)
3[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide(1 : 1) succinate	35*
D-Glucose	3000
Aspartame	10
Purified water	q.s.+

*Equivalent to 25mg base

+The water does not appear in the final product

The active ingredient and D-glucose are mixed together and granulated by the addition of purified water. The granules obtained after mixing are dried and passed through a screen, and the resulting granules are then mixed with the aspartame. The mixture is filled into aluminium foil sachets which are sealed in conventional manner.

The contents of the sachet are dissolved in a glass of drinking water immediately prior to oral administration.

Example 3

Powder for Oral Administration	Unit dose

	(mg per sachet)
N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide hydrochloride	22.2*
D-glucose	1000
Aspartame	40
Flavour	16

*Equivalent to 20mg base

The ingredients are thoroughly mixed together in a suitable blender under anhydrous conditions and filled into an aluminium foil sachet. The sachet is sealed after filling in conventional manner.

The contents of the sachet are dissolved in a glass of drinking water immediately prior to oral administration.

Example 4

Granules for Oral Administration	Unit dose (mg per sachet)
N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide hydrochloride	5.55*
D-glucose	3000
Aspartame	10
Purified water	q.s.+

*Equivalent to 5mg base

+The water does not appear in the final product

The active ingredient and lactose are mixed together and granulated by the addition of purified water. The granules obtained after mixing are dried and passed through a screen, and the resulting granules are then mixed with the

aspartame. The mixture is filled into aluminium foil sachets and sealed in conventional manner.

The contents of the sachet are dissolved in a glass of drinking water immediately prior to oral administration.

Example 5

Effervescent Tablet	Unit dose (mg per sachet)
3[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide(1 : 1) succinate	140.0*
Sodium bicarbonate	656.4
Monosodium citrate anhydrous	659.5
D-galactose	3000
Aspartame	40.0
Polyvinylpyrrolidone	32.0
Sodium benzoate	48.0
Orange flavour IFF 29G44	16.0
Lemon flavour IFF 29M194	8.0
Absolute alcohol for granulation	

*Equivalent to 100mg base

The active ingredient, anhydrous monosodium citrate, sodium bicarbonate and aspartame are mixed together and granulated by the addition of a solution of the polyvinylpyrrolidone in the alcohol. The granules obtained after mixing are dried and passed through a calibrator, and the resulting granules are then mixed with the D-galactose, sodium benzoate and flavourings. The granulated material is compressed into tablets using an alternative machine fitted with 20mm punches.

A rotative machine fitted with 20mm punches may also be used for tabletting.

Example 6

Sterile Formulation for Intranasal Administration

3-[2-Dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide	100mg
D-glucose	500mg
Sulphuric Acid (concentrated)	21.2mg
Sodium Hydroxide BP	qs to pH 5.4-5.6
Water for Injections B.P.	to 1ml

The active compound and D-glucose is dissolved in the sulphuric acid previously diluted with water. The solution is made up to approximately 90% volume. The solution pH is adjusted to 5.5 with sodium hydroxide solution and the solution finally made up to volume. The solution pH is remeasured and adjusted if necessary.

The solution may be packaged for intranasal administration, for example by filling into vials, sealing and sterilising the vials by autoclaving at 121°C for not less than 15 minutes.

Example 7

Preserved Formulation for Intranasal Administration

3-[2-Dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide	100mg
D-glucose	500mg
Sulphuric Acid (concentrated)	21.2mg

Phenylethyl Alcohol USP	4mg
Benzalkonium Chloride USNF	0.2mg
Sodium Hydroxide BP	qs to pH 5.4-5.6
Purified Water BP	to 1ml

The active compound and D-glucose is dissolved in the sulphuric acid previously diluted with water. Phenylethyl alcohol and benzalkonium chloride are added and the solution is made up to approximately 90% of volume. The solution pH is adjusted to 5.5 with sodium hydroxide solution and the solution finally made up to volume. The solution pH is remeasured and adjusted if necessary.

In a similar manner further preserved formulations are prepared containing 5, 10, 50, 100, 200 and 400 $mgml^{-1}$ of the active compound.

Formulations are administered in unit dose volumes of 100µl to either one or both nostrils of patients suffering from a moderate or severe migraine attack to deliver a dose of 1, 5, 10, 20 or 40mg of the active compound.

Example 8

Sterile Formulation for Intranasal Administration

N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide hydrochloride	1 or 2.5 or 5 or 10mg
D-glucose	50mg
Purified Water B.P.	To 1ml

100 microlitres of the above solution is administered to provide a 0.1, 0.25, 0.5 and 1mg dose respectively. The glucose level may be used in the range from 10-100mg (1-10% w/v).

Example 9

Solution for Intranasal Administration

N-methal-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethane sulphonamide	168.71mg to 1mL
5% (w/v) D-glucose solution	

100 microlitres of the above solution is administered to provide a 12mg dose of the free base.

Biological Examples

The rate of absorption of naratriptan in an intranasal formulation containing a paracellular absorption enhancer was compared with the rate of absorption of an aqueous formulation of naratriptan in dogs.

Test Formulations:

A		B	
Naratriptan maleate	168.71mg	Naratriptan maleate	168.71mg
Water	to 1ml	5% (w/v) D-glucose solution	to 1ml

Method

Four male dogs were placed in individual cages. Each dog was given an intranasal dose of 100µL of Formulation A. Blood samples were taken from each dog by venepuncture of the cephalic or jugular vein into heparinised tubes at approximately 5, 10, 15, 20, 30 and 40 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24,

32 and 48 hours after dosing. Each sample was centrifuged within 1 hour after collection and the plasma obtained was stored frozen prior to analysis. After a period of 14 days the procedure was repeated, giving each dog a 100μL dose of Formulation B.

The plasma samples were analysed for the presence of naratriptan and T_{max} and the absorption half-life were calculated for Formulation A and Formulation B.

Results

The results are shown in Tables I and II below:

Table I

	T_{max} (h) Animal No.				Mean ± SD
	1	2	3	4	
Formulation A	2.0	1.0	0.5	0.67	0.5 - 2.0
Formulation B	0.67	1.5	0.33	0.33	0.33 - 1.5

Table II

	Absorption half-life (h) Animal No.				Mean ± SD
	1	2	3	4	
Formulation A	0.26	0.20	0.13	0.14	0.18 + 0.06
Formulation B	0.17	0.12	0.04	0.05	0.10 + 0.06

These results indicate that the rate of absorption of naratriptan when administered intranasally as the maleate salt is increased in the presence of D-glucose.

CLAIMS

1. The use of a $5HT_1$-like receptor agonist and one or more paracellular absorption enhancers in the manufacture of medicaments for simultaneous, separate or sequential use for the treatment of cephalic pain, eg migraine and elevated, intraocular pressure.

2. The use of a $5HT_1$-like receptor agonist and one or more paracellular absorption enhancers in the manufacture of medicaments for simultaneous, separator sequential use for the treatment of cephalic pain, eg migraine and elevated, intraocular pressure characterised that the paracellular absorption enhancer significantly enhances the absorption of the $5HT_1$-like receptor agonist.

3. The use according to claim 1 or claim 2 wherein the $5HT_1$-like receptor agonist is sumatriptan, naratriptan or 4-[3-(trans-3-dimethylaminocyclobutyl)-1H-indol-5-ylmethyl]-(4S) oxazolidin-2-one or a physiologically acceptable salt thereof.

4. The use according to any of claims 1 to 3 wherein the $5HT_1$-like receptor agonist is naratriptan or a physiologically acceptable salt thereof.

5. The use according to any of claims 1 to 4 wherein the medicaments are administered intranasally.

6. The use according to any of claims 1 to 5 wherein the paracellular absorption enhancer is D-glucose or D-galactose.

7. A method of treatment of cephalic pain, eg migraine and elevated intraocular pressure in a mammal comprising orally or intranasally administering an effective amount of a pharmaceutical composition comprising a $5HT_1$-like receptor agonist, or a physiologically acceptable salt thereof, and one or more paracellular absorpti on enhancers.

8. A method of enhancing the rate of absorption of a $5HT_1$-like receptor agonist or a physiologically acceptable salt thereof following oral or intranasal administration by simultaneous, separate or sequential administration of the $5HT_1$-like receptor agonist with one or more paracellular absorption enhancers.

9. A method according to claim 7 or claim 8 wherein the $5HT_1$-like receptor agonist and the paracellular absorption enhancer are administered simultaneously.

10. A method according to any of claims 7 to 9 wherein the $5HT_1$-like receptor agonist and the paracellular absorption enhancer are administered intranasally.

11. A method according to any of claims 7 to 10 wherein the $5HT_1$-like receptor agonist is naratriptan or a physiologically acceptable salt thereof.

12. A pharmaceutical composition for oral or intranasal administration comprising a $5HT_1$-like receptor agonist and one or more paracellular absorption enhancers.

13. A composition according to claim 12 wherein the $5HT_1$-like receptor agonist is sumatriptan, naratriptan or 4-[3-(trans-3-dimethylaminocyclobutyl)-1H-indol-5-ylmethyl]-(4S) oxazolidin-2-one.

14. A composition according to claim 12 or claim 13 wherein the $5HT_1$-like receptor agonist is naratriptan in the form of its maleate or aspartate hydrochloride salt.

15. A composition according to any of claims 12 to 14 for intranasal administration.

16. A composition according to any of claims 12 to 15 wherein the paracellular absorption enhancer is D-glucose for D-galactose.

17. A composition according to any of claims 12 to 16 wherein the ratio of $5HT_1$-like receptor agonist to paracellular absorption enhancer is in the range of 1:1 to 1:1000 by weight.

INTERNATIONAL SEARCH REPORT

In' tional Application No
PCT/GB 97/00663

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/40 A61K31/435 A61K31/42 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 162 522 A (GLAXO GROUP LTD) 5 February 1986 cited in the application see page 9 - page 11 ---	1-3,5, 7-10,12, 13,15,17
X	GB 2 208 646 A (GLAXO GROUP LTD) 12 April 1989 cited in the application see page 24 - page 28 ---	1-5, 7-13,15, 17
X	WO 95 20588 A (WELLCOME FOUND ;GLEN ROBERT CHARLES (GB); FOSTER CHRISTOPHER JAMES) 3 August 1995 cited in the application see page 39 - page 41 ---	1-3,7-9, 12,13,17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
20 May 1997	30. 05. 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer TRIFILIEFF-RIOLO, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/GB 97/00663

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 308 181 A (NOVO INDUSTRI AS) 22 March 1989 see page 3, left-hand column, line 15 - line 53	1-17
A	INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 114, no. 2, 1995, pages 137-149, XP000673693 MOUNIR MESIHA ET AL.: "increased oral absorption of insulin by medium viscosity hydroxypropyl cellulose" see the whole document	1-17

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB 97/00663

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.
because they relate to subject matter not required to be searched by this Authority, namely.

Remark: Although claim(s) 7-11
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.. 1,2,5,7-10,12,15,17
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

In view of the large number of compounds which are defined by the wording of the claims, the search has been performed on the general idea and compounds mentioned in the examples of the description.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos..

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir tional Application No
PCT/GB 97/00663

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